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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/275,883	03/25/1999	WOLFGANG A. RENNER	1700.0020001	1349

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EXAMINER	
SCHNIZER, RICHARD A	
ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 01/29/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/275,883	RENNER ET AL.	
	Examiner	Art Unit	
	Richard Schnizer, Ph. D	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondenc address --

Peri d for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *17 December 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *75-78,81-84,86-103,105-107 and 109-145* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) *102* is/are allowed.

6)☐ Claim(s) *75-78,81-84,86-101,103,105-107 and 109-145* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *25 March 1999* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

A Notice of Appeal, responsive to a non-final rejection, was received and entered on 12/17/03.

Claims 75-78, 81-84, 86-103, 105-107, and 109-145 are pending and under consideration in this Office Action.

Drawings

The Drawings stand objected to for the reasons of record in the Notice of Draftsperson's Drawing Review (Form 948) attached to Paper No. 22.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 75-78, 81-84, 86-101, 103, 105-107, and 109-145 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, for the reasons of record in Paper Nos. 11, 15, and 19.

The claimed invention encompasses the genus of DNA molecules comprising an open reading frame encoding a non-cytopathic, temperature-sensitive alphaviral replicase, wherein the non-cytopathicity and temperature-sensitivity are conferred by one or more mutations in the genes encoding the non-structural proteins of the replicase.

Applicant is referred to the interim guidelines on written description published December 21, 1999 in the Federal Register, Volume 64 Number 244, pp. 71427-71440 (also available at www.uspto.gov). The following passage is particularly relevant.

> The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between structure and function structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus.
>
> A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within a genus, one must describe a sufficient number of species to reflect the variation within the genus. What constitutes a "representative number" is an inverse function of the skill and knowledge in the art. Satisfactory disclosure of a "representative number" depends on whether one of skill in the art would recognize that applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. In an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus.

The central issue in this analysis is whether Applicant has disclosed a number of species which is representative of the claimed genus. Applicant discloses a single open reading frame encoding a Sindbis virus RNA-dependent RNA polymerase. This polymerase comprises a P726S nsP2 mutation in combination with a G153E nsP4 mutation. The P726S nsP2 and G153E nsP4 mutations are the structural features which are required to render the Sindbis virus polymerase both temperature sensitive and non-cytopathic. See paragraph bridging pages 21 and 22; page 22, lines 17 and 18; and page 23, lines 22-24. Temperature sensitivity and non-cytopathicity are the necessary common attributes which the polymerase must possess in order to qualify as a member of the claimed genus. However, the specification has failed to disclose what mutations are required to render any other RNA-dependent RNA polymerase both

temperature sensitive and non-cytopathic, or what other mutations could confer this phenotype on the Sindbis virus polymerase. The state of the art of the prediction of protein function based on protein structure is not sufficiently advanced to predict *a priori* what mutations will confer temperature sensitivity or non-cytopathicity on a given RNA-dependent RNA polymerase, so it falls to the specification to provide this information. One of skill in the art appreciates that a wide variety of alphaviral RNA-dependent RNA polymerase is known in the art. In view of this recognized variety, and in view of the uncertainty associated with predicting which amino acid substitutions will confer temperature sensitivity and non-cytopathicity on a given polymerase, the disclosure of only a single species is considered insufficient to convey to one of skill in the art that applicant was in possession of the claimed genus at the time of the invention.

The courts have found that merely describing the functional characteristics of a protein encoded by a particular nucleic acid is insufficient to adequately describe the genus of nucleic acids encoding that protein. A gene is a chemical compound, albeit a complex one, and it is well established in our law that conception of a chemical compound requires that the inventor be able to define it so as to distinguish it from other materials, and to describe how to obtain it. See Oka, 849 F.2d at 583, 7 USPQ2d at 1171. Conception does not occur unless one has a mental picture of the structure of the chemical, or is able to define it by its method of preparation, its physical or chemical properties, or whatever characteristics sufficiently distinguish it. It is not sufficient to define it solely by its principal biological property, e.g., non-cytopathic, temperature-sensitive alphaviral replicase, because an alleged conception having no more specificity

than that is simply a wish to know the identity of any material with that biological property. When an inventor is unable to envision the detailed constitution of a gene so as to distinguish it from other materials, conception has not been achieved until reduction to practice has occurred, i.e., until after the gene has been isolated. Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016, 1021 (Fed. Cir. 1991). The instant application does not provide a written description that would allow one of skill in the art to immediately envisage the specific structure for Sindbis virus non-cytopathic, temperature-sensitive replicase, or for the broader genus of alphaviral non-cytopathic, temperature-sensitive replicase. *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed* (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (See *Vas-Cath* at page 1116). As there is disclosure of only a single species of the claimed genus of polynucleotides, and the art is unpredictable, the skilled artisan cannot envision the detailed chemical structure of any other species of the claimed genus, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The nucleic acid itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at

1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

The limited information provided in the specification is not deemed sufficient to reasonably convey to one skilled in the art that Applicants were in possession of the broadly claimed polynucleotides at the time the application was filed. Thus it is concluded that the written description provision of 35 U.S.C 112, first paragraph, is not satisfied for the claimed polynucleotides. Applicants are reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C 112 is severable from its enablement provision (see page 1115).

Response to Arguments

Applicant's arguments filed 12/17/03 have been fully considered as they apply to the rejection above but they are not persuasive.

Applicant considers the issue of written description at pages 2-10 of the response. As noted above, the central issue for consideration is whether or not the specification has described a representative number of species of the claimed invention. The specification has described only a single species by complete structure and reduction to practice. Because the genus embraces any nucleic acid encoding any temperature sensitive and non-cytopathic alphaviral replicase, and because the art of protein structure/function relationships is unpredictable, description of additional species by relevant identifying characteristic is warranted. Applicant argues at page 7 of the response that the structural and functional characteristics of the claimed nucleic acids are described adequately to satisfy the requirements of 35 USC 112 first paragraph regarding relevant identifying characteristics. The basis of this argument is that the specification discloses that 1) the nucleic acids must encode a temperature sensitive alphaviral replicase (function), and that 2) this function is bestowed by one or more mutations in the genes encoding non-structural proteins of the alphavirus (structure). However, even the narrowest of the rejected claims only limits the structure of the mutations by limiting the identity of the genes in which the mutations must occur. There are no limitations whatsoever on where in each gene the mutations must occur, or what type of mutation is required to yield the desired function. Because of the unpredictable nature of the effects of amino acid substitutions on protein function, established previously, one of skill in the art would not consider the mere identification of a gene which is to be mutated as a relevant identifying characteristic of a type of mutation, e.g. a mutation rendering an alphaviral replicase temperature sensitive and or non-cytopathic. Instead, the description requirement could be satisfied by the identification of specific amino acid positions of a protein at which the required types of mutations can be made, and a description of the types of amino acid substitutions that can be used to

obtain the desired function, such that one of skill in the art would be convinced of some correlation between structure and function. The specification fails to supply such information, other than the single example of the P726S nsP2, G153E nsP4 species.

The Office has acknowledged that a variety of temperature sensitive alphaviral replicase mutations were known in the art at the time of the invention. However, at the time of the invention, only a single mutation conferring a non-cytopathic phenotype on an alphaviral replicase was known, i.e. P726S of nsp2. It is noted that at page 4 of the response, Applicant cites a portion of the specification that might lead one to believe otherwise. This passage cites the Weiss (1980) and Dryga (1997) publications. However, these publication disclose only the nsp2 P726S mutation, consequently the specification discloses only a single example of a single mutation conferring a non-cytopathic phenotype on an alphaviral replicase, a single example of an alphaviral replicase that is both temperature sensitive and noncytopathic, and no examples at all of an alphaviral replicase in which the required functional characteristics are cause by only a single mutation, such as is embraced by the claims.

At pages 6 and 8 of the response Applicant notes that the post-filing art gives examples of mutations other than nsp2 P726S that cause the replicase to be noncytopathic. However, each of these mutations was obtained by random mutagenesis after the time the invention was filed, and Applicant has failed to show that there was any known or described correlation between structure and function of alphaviral replicases that would have conveyed to one of skill in the art that Applicant was in possession of these molecules at the time of filing. Applicant argues that the Declaration of Dr. Schlesinger indicates that those of ordinary skill in the art could easily obtain non-cytopathic and temperature-sensitive mutations. However, Applicant is reminded that the description and enablement requirements are severable, so the

contention that mutations are easily made does not address the issue of whether or not they have been adequately described. As the specification describes only a single species by complete structure, description of relevant identifying characteristics is warranted. However, no guidance with regard to the particular function of any region of any non-structural protein is provided by the specification or the prior art of record such that one of skill in the art could envisage any single mutation, other than nsp2 P726S, that would cause the required noncytophathic effect. It has been established by the Office that the art of protein structure and function prediction is highly unpredictable. The guidelines on written description published December 21, 1999 in the Federal Register, Volume 64 Number 244, pp. 71427-71440 (also available at www.uspto.gov) state:

> In an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus.

Additionally, the courts in *In re Shokal*, 113 USPQ 283 (CCPA 1957) found that

> It appears to be well settled that a single species can rarely, if ever, afford sufficient support for a generic claim. In re Soll, 25 C.C.P.A. (Patents) 1309, 97 F.2d 623, 38 USPQ 189; In re Wahlforss et al., 28 C.C.P.A. (Patents) 867, 117 F.2d 270, 48 USPQ 397. The decisions do not however fix any definite number of species which will establish completion of a generic invention and it seems evident therefrom that such number will vary, depending on the circumstances of particular cases. Thus, in the case of small genus such as the halogens, consisting of four species, a reduction to practice of three, or perhaps even two, might serve to complete the generic invention, while in the case of a genus comprising hundreds of species, a considerably larger number of reductions to practice would probably be necessary.

The claimed genus embraces mutations in any of four structurally distinct genes in any known alphavirus. The claims are supported by a description of only a single species. Therefore, one of skill in the art could not conclude that Applicant was in possession of the claimed genus at the time the invention was filed.

For these reasons the rejection is maintained.

Enablement

Claims 75-79, 81-84, 86-101, 103, 105-107, and 109-136 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a DNA molecule encoding the Sindbis virus non-cytopathic, temperature-sensitive alphaviral replicase with P726S nsp2 and G153E nsp4 mutations, does not reasonably provide enablement for DNA molecules encoding any other alphaviral non-cytopathic, temperature-sensitive alphaviral replicase. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims for the reasons of record in Paper Nos. 11, 15, 19, 22, and 26.

The claims encompass nucleic acid molecules encoding a non-cytopathic, temperature-sensitive alphaviral replicase, methods of using the nucleic acids, alphaviral particles comprising the nucleic acids, and cells comprising the nucleic acids. The molecules encode an open reading frame which must undergo at least one RNA-dependent RNA polymerase-mediated replication event in order to be translatable.

As discussed above, the specification discloses only a single example of a non-cytopathic, temperature-sensitive RNA-dependent RNA polymerase, yet the claims encompass the entire genus rather than just the single disclosed species. The prior art teaches several Sindbis virus polymerases which are temperature sensitive. The art teaches several isolates of alphaviruses with non-cytopathic effects, but only a single alphaviral replicase mutation conferring non-cytopathicity had been identified at the time of filing, i.e. nsp2 P726S. The scope of the claims is not limited to this single known non-cytopathic Sindbis virus replicase, but embraces all such mutations that could ever occur. The specification fails to provide any guidance as to what amino acids to alter in

any non-structural protein in order to obtain a non-cytopathic replicase other than one comprising nsp2 P726S. The specification fails to disclose any example of a polymerase, other than that encoded by SEQ ID NO:1, which is both temperature sensitive and non-cytopathic. Further, while it is simple to construct nucleic acids which would comprise both types of mutations, the characteristics of these novel polypeptides would be highly unpredictable, as stated in the previous office actions. The reason for this is that it is not currently possible to accurately predict the effects of mutations on the function of proteins. For example, Rudinger (In peptide Hormones, J.A. Parsons Ed. University Park press, Baltimore, 6/1996) teaches that "[t]he significance of particular amino acids and sequences for different aspects of biological activity cannot be predicted a priori but must be determined from case to case by painstaking experimental study." See page 6, last paragraph. Furthermore, Schnizer et al (Arch Biochem Biophys. 1996 Feb 1;326(1):126-36) teach an example in which mutations of two separate amino acids of the yeast F1-ATPase beta subunit were combined and produced totally unpredictable results. Specifically, one mutation at position 203 and five different mutations at position 211 were found to inactivate and destabilize the F1-ATPase complex when expressed separately. However, when the position 203 mutation was combined with and any one of the position 211 mutations in the same construct, destabilization was suppressed and activity was restored to the ATPase complex. See abstract. While this result may allow certain conclusions to be drawn about structural and functional relationships within the ATPase, it could not have been predicted *a priori*. Similarly the effects of combining mutation in the Sindbis virus polymerases cannot be predicted a priori. One might argue that it would not be undue experimentation to express and assay each construct individually and thereby determine empirically which ones encoded polymerases of the desired phenotype. However, as set forth in In re

Fisher, 166 USPQ 18 (CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> that scope of claims must bear a reasonable correlation to scope of enablement provided by the specification to persons of ordinary skill in the art; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement varies inversely with degree of unpredictability of factors involved.

In this case, the art is not sufficiently advanced to allow the prediction of mutations that will cause non-cytopathicity, or to allow the prediction of the effects of combining temperature-sensitive and non-cytopathic mutations. Furthermore, Applicant has disclosed mutations only of a Sindbis virus replicase, whereas the claims encompass replicases from all alphaviruses. One of skill in the art could not predict which, if any, of these replicases could be mutated to be appropriately temperature sensitive and non-cytopathic, or what mutations would be required for this.

In view of the unpredictability of polypeptide structure-function relationships, the failure of the specification to disclose more than one example of a Sindbis virus temperature sensitive, non-cytopathic RNA-dependent RNA polymerase, and the failure of the specification to provide any guidance as to what mutations other than nsp2 P726S will provide a non-cytopathic replicase, one of skill in the art could not make the invention commensurate in scope with the claims.

Response to Arguments

Applicant's arguments filed 12/17/03 have been fully considered as they apply to the rejection above but they are not persuasive.

Applicant's arguments are based on the position that it is not necessary to be able to predict in advance what are the structural characteristics of the claimed molecules because they can be isolated by functional screening of randomly generated mutants. Applicant argues that this is routine in the art. However, at the time of the invention, only a single noncytopathic replicase mutation was known, so arguments that such mutations were routinely discovered are unpersuasive. No evidence has been presented to indicate that, at the time the invention was filed, it was routine in the art to isolate noncytopathic replicase mutants by any technique, including random or directed mutagenesis. Applicant asserts that the Declaration of Dr. Schlesinger supports the use of random mutagenesis and screening for this purpose. However, as discussed previously, the court has found that although a declaration is considered to be evidence itself that must be considered, the weight to give a declaration will depend upon the amount of factual evidence the declaration contains to support the conclusion of enablement. In re Buchner, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991) ("expert's opinion on the ultimate legal conclusion must be supported by something more than a conclusory statement"). In this case the Declaration provides no factual evidence whatsoever, and is only a statement of Declarant's beliefs. As such it is insufficient to overcome the prima facie case established by the Office.

Applicant argues at page 11 of the response that the Examiner did not explain why methods of random mutagenesis and phenotypic screening would not have been used in the context of the present invention. In response the Office notes that this is not what is at issue. What is at issue is whether or not the specification reasonably teaches how to make and use the invention commensurate in scope with the claims. Applicant's attention is directed to the rejection, which indicates that phenotypic screening of random mutations is undue in an unpredictable art. Applicant has not shown why the

Office's reliance on In Re Fisher in this regard is incorrect, and has not provided any evidence that, at the time the invention was filed, one of skill in the art would not have had to perform undue experimentation in order to obtain noncytopathic replicases other than the single one disclosed in the specification, i.e. no evidence has been presented as to why a trial and error approach does not represent undue experimentation in the unpredictable art of making non-cytopathic alphaviral replicases. For these reasons the rejection is maintained.

Conclusion

Claim 102 is allowable.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action. Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:20 AM and 3:50 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Andrew Wang, can be reached at 703-306-3217 before 2/22/04, and at 571-272-0811 after 2/22/04. The official central fax number is 703-872-9306 until further notice. Inquiries of a general nature or relating to the status of the application should be directed to the Patent Analyst Trina Turner whose telephone number is 571-272-0564.

Amy Nelson for
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